Synthesis of 3-Arylamino-4(3*H*)quinazolinone Derivatives from 1-Acetyl- or 1-Ethoxycarbonylmethylene-2-arylhydrazines

Pasqualina Trimarco

Istituto di Chimica Organica della Facolta' di Farmacia, Universita' di Milano, Viale Abruzzi 42, 20131 Milano, Italy

and

Cristina Lastrucci

Istituto di Chimica Industriale dell' Universita', Via Golgi 19, 20133 Milano, Italy

Received February 23, 1976

By reacting 1-acetyl- or 1-ethoxycarbonylchloromethylene-2-arylhydrazines (**2a-c**) with anthranilic acids (**1a-b**) the corresponding *C*-acetyl- or *C*-ethoxycarbonylcarbohydrazonamide derivatives (**3a-d**) were obtained. Ring closure of the carbohydrazonamides with acetic anhydride afforded 2-carboethoxy- or 2-acetyl-3-arylamino-4(3*H*)quinazolinones (**4a-d**). The ester derivatives undergo basic hydrolysis with decarboxylation to 3-arylamino-4(3*H*)quinazolinones (**5a-b**).

J. Heterocyclic Chem., 13, 913 (1976).

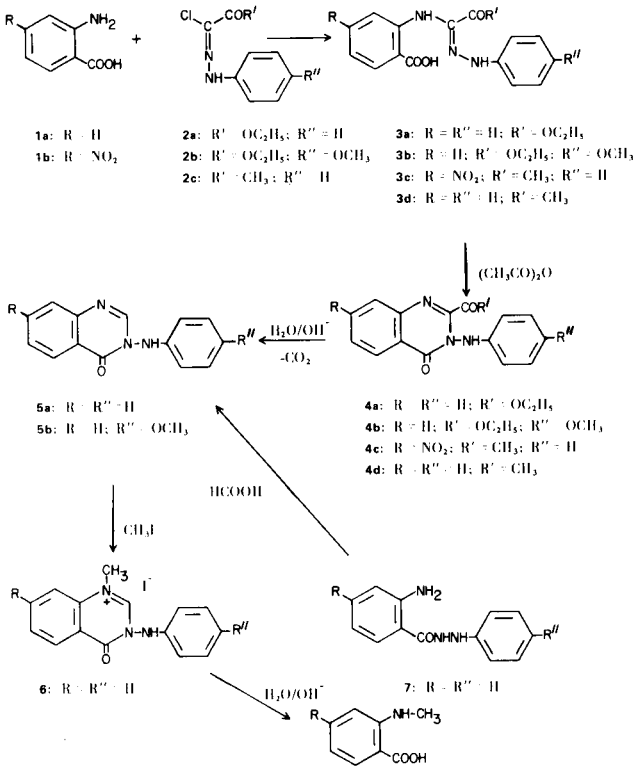
The synthesis of heterocyclic compounds by the reaction between 1-acetyl- or 1-ethoxycarbonylchloromethylene-2-arylhydrazines and anthranilic acid or its derivatives has been investigated. In principle, this reaction could afford quinazolinone derivatives or benzotriazepine derivatives. Particularly, few 3-arylamino-2-acylsubstituted quinazolinones are reported in the literature and could be of interest in view of their structural analogy with 3-aryl-2-alkyl-4(3*H*)quinazolinones which are known to have sedative activity (1).

The 1-acetyl- and 1-ethoxycarbonylchloromethylene-2-arylhydrazines, **2a-c**, readily react with anthranilic acids (**1a-b**) in ethanol solution in the presence of triethylamine leading to the corresponding carbohydrazonamides, **3a-d**, whose structure is supported by analytical and spectroscopic (ir and nmr) data.

The ring closure of carbohydrazonamides **3a-d** occurs spontaneously and slowly in chloroform solution (probably owing to the catalytic effect of the acidity present in this solvent). Alternatively, a brief heating in acetic anhydride of **3a-d** quickly results in the same ring closure.

The 2-carboethoxysubstituted quinazolinones, **4a-b**, easily undergo basic hydrolysis with concurrent decarboxylation affording the corresponding 2-unsubstituted quinazolinones, **5a-b**. The quinazolinone structure of **5a-b** and hence of the full series **4a-d** can be assigned from the nmr spectra and ir data which are in good agreement with those reported in the literature (2).

Particularly, the ir spectrum of **5b** is superimposable to that of 3-[*N*-(4-methoxyphenyl)amino-4(3*H*)quinazo-



linone prepared by Csúrős, *et al.* (3).

Compound **5a** undergoes a quaternarization reaction with methyl iodide giving the salt **6** whose quaternary ammonium character is confirmed also by the low field shift (4.18 δ) of the methyl signal in the nmr spectrum. On basic hydrolysis **6** affords *N*-methylanthranilic acid (**8**) thus demonstrating the quaternarization position. The 3-anilino-4(3*H*)quinazolinone, **5a**, has been also synthetized by treatment with formic acid of *N*-(2-aminobenzoyl)-*N'*-phenylhydrazine (**7**) (4).

EXPERIMENTAL

Melting points are uncorrected. The nmr spectra were recorded with Varian A-60 and JNM-C-60-HL spectrometers at 60 MHz. Chemical shifts are given in ppm relative to internal TMS (δ). Ir spectra were recorded with Perkin-Elmer Infracord and Beckman 8 spectrometers (nujol, cm^{-1}).

General Method for the Preparation of C-Acetyl- and C-Ethoxycarbonylcarbohydrazonamides (**3a-d**).

The anthranilic acid (**1a-b**, 0.01 mole) was dissolved in 95% ethanol (40-80 ml.) together with the 1-acetyl- or 1-ethoxycarbonylchloromethylene-2-arylhydrazine (6) (**2a-c**, 0.01 mole). Triethylamine (0.01 mole) was added and the mixture refluxed (4-18 hours) until complete reaction (tlc). Then, the reaction mixture was diluted with water (25-50 ml.). The precipitate formed was filtered and recrystallized.

Compound **3a**.

This compound was a yellow powder, m.p. 179-180° (from ethanol), yield 20%; ir: 3340, 3260 (NH); 1715, 1650 (CO); nmr (hexadeuteriodimethylsulfoxide): 1.22 (3H, t, CH_3); 4.18 (2H, q, CH_2); 6.15-8.10 (10H, m, aromatic and NH); 9.23 (1H, s, NH); 9.98 (1H, s, OH).

Anal. Calcd. for $C_{17}H_{17}N_3O_4$: C, 62.37; H, 5.24; N, 12.84. Found: C, 62.65; H, 5.00; N, 13.07.

Compound **3b**.

This compound had m.p. 188° (from ethanol), yield 28%; ir: 3320, 3220 (NH); 1710, 1650 (CO); nmr (hexadeuteriodimethylsulfoxide): 1.20 (3H, t, CH_3); 3.70 (3H, s, OCH_3); 4.20 (2H, q, CH_2); 7.14 (9H, m, aromatic and NH).

Anal. Calcd. for $C_{18}H_{19}N_3O_5$: C, 60.49; H, 5.36; N, 11.76. Found: C, 60.21; H, 5.11; N, 11.50.

Compound **3c**.

This compound had m.p. 223° (from ethanol), yield 50%; ir: 3260 (NH); 1685, 1640 (CO); nmr (hexadeuteriodimethylsulfoxide): 2.50 (3H, s, $COCH_3$); 6.70-8.20 (9H, m, aromatic and NH); 9.40 (1H, NH); 10.05 (1H, s, OH).

Anal. Calcd. for $C_{16}H_{14}N_4O_5$: C, 56.14; H, 4.12; N, 16.37. Found: C, 56.08; H, 3.97; N, 16.08.

Compound **3d**.

This compound had m.p. 199-200° (from ethanol), yield 58%; ir: 3265, 3175 (NH); 1695, 1690 (CO); nmr (hexadeuteriodimethylsulfoxide): 2.50 (3H, s, $COCH_3$); 6.00-8.00 (10H, m, aromatic and NH); 9.25 (1H, NH); 9.98 (1H, s, OH).

Anal. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.63; H, 5.09; N, 14.14. Found: C, 65.01; H, 5.12; N, 13.88.

General Method for the Preparation of 2-Acetyl- and 2-Carboethoxy-3-arylamino-4-(3*H*)quinazolinones (**4a-d**).

The carbohydrazonamide (**3a-d**, 0.005 mole) was dissolved in acetic anhydride (15 ml.) and refluxed for 20 minutes. The reaction mixture was evaporated under reduced pressure and the residue was taken up with isopropyl ether (15 ml.). The mixture was chilled in ice and filtered. The crystalline product was recrystallized from benzene/petroleum ether (b.p. 40-60°).

Compound **4a**.

This compound had m.p. 153-154°, yield 80%; ir: 3300 (NH); 1750, 1715 (CO); nmr (deuteriochloroform): 1.16 (3H, t, CH_3); 4.32 (2H, q, CH_2); 6.65-8.27 (10H, m, aromatic and NH).

Anal. Calcd. for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.59. Found: C, 65.63; H, 4.81; N, 13.47.

Compound **4b**.

This compound had m.p. 135°, yield 75%; ir: 3300 (NH); 1740, 1690 (CO); nmr (deuteriochloroform): 1.13 (3H, t, CH_3); 3.70 (3H, s, OCH_3); 4.28 (2H, q, CH_2); 6.40-8.20 (8H, m, aromatic); 9.12 (1H, s, NH).

Anal. Calcd. for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.91; H, 4.77; N, 12.24.

Compound **4c**.

This compound had m.p. 207-209°, yield 40%; ir: 3340 (NH); 1710, 1650 (CO).

Anal. Calcd. for $C_{16}H_{12}N_4O_4$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.57; H, 3.52; N, 16.93.

Compound **4d**.

This compound had m.p. 151-152°, yield 65%; ir: 3333 (NH); 1710 (CO); nmr (deuteriochloroform): 2.54 (3H, s, $COCH_3$); 6.60-8.32 (10H, m, aromatic and NH).

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.05. Found: C, 69.00; H, 4.37; N, 14.98.

3-Anilino-4(3*H*)quinazolinone (**5a**).

a) From **4a**.

Potassium hydroxide (0.5 g.) was dissolved in 95% ethanol (10 ml.) and **4a** (0.3 g.) was added and stirred for 30 minutes. The reaction mixture was diluted with water (10 ml.) and acidified to litmus with concentrated hydrochloric acid. The precipitate was filtered, washed with water and recrystallized from ethanol, m.p. 170-171°, yield 35%; ir: 3200 (NH); 1680 (CO); nmr (deuteriochloroform): complex multiplet at 6.60-8.40 (aromatic and NH).

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 71.16; H, 4.67; N, 17.48.

b) From 2-Amino-2'-phenylbenzhydrazide (**7**).

Compound **7** (7) (0.75 g.) was dissolved in 99% formic acid (10 ml.). After 16 hours refluxing the excess formic acid was evaporated and the residue taken up in isopropyl acetate and filtered, m.p. 169-170°.

3-(4-Methoxyphenylamino)-4(3*H*)quinazolinone (**5b**).

This compound was prepared essentially as described for **5a** from **4b** (0.7 g.). The product was filtered and purified through chromatography on a silica column (eluent: benzene/ethyl acetate 95:5) and recrystallization from ethanol, m.p. 152°, yield 50%. This product shows the same properties (ir and m.p.) already reported in the literature (2).

1-Methyl-3-anilino-4(3*H*)quinazolinonium Iodide (**6**).

In a small autoclave, **5a** (0.25 g.) was reacted at 100° for 48 hours with methyl iodide (22 ml.). Then the autoclave was cooled, and the crystalline precipitate was filtered with suction and recrystallized from aqueous ethanol, pale yellow crystals, m.p. 204°, yield 60%; ir: 3200 (NH); 1735 (CO); nmr (hexadeuteriodimethylsulfoxide): 4.18 (3H, s, CH_3); 7.10-8.10 (10H, m, aromatic and NH).

Anal. Calcd. for $C_{15}H_{13}IN_3O$: C, 47.63; H, 3.46; N, 11.11. Found: C, 47.67; H, 3.40; N, 10.95.

N-Methylanthranilic Acid (**8**).

The quaternary ammonium salt, **6**, was hydrolyzed by refluxing 3 hours with 10% sodium hydroxide in ethanol. After cooling the solvent was evaporated and the residue extracted with ether. The aqueous layer was neutralized with 10% hydrochloric acid. The precipitate was filtered, recrystallized from ethanol and identified as *N*-methylanthranilic acid by comparison with an authentic sample.

REFERENCES AND NOTES

(1) J. R. Boissier, C. Dumont and C. Malen, *Thérapie*, **13**, 30 (1968); L. G. Zilbermints, *Farmakol. Toksikol.*, **27**, 413 (1964); P. N. Saxena, B. K. Khanna, *Indian J. Med. Res.*, **46**, 63 (1958).

(2) H. Culbertson, J. C. Decius, B. E. Christensen, *J. Am. Chem. Soc.*, **74**, 4834 (1952); Z. Csürös, R. Soós, J. Pálinkás and I. Bitter, *Acta Chim. Acad. Sci. Hung.*, **63**, 215 (1970).

(3) Z. Csürös, R. Soós, I. Bitter and J. Pálinkás, *ibid.*, **69**, 361 (1971).

(4) In our hands this ring closure could be performed only under conditions somewhat different from those described in the literature (5). Moreover, the melting point reported for **5a** is different from that of our product.

(5) S. Thode, *J. Prakt. Chem.*, [2], **69**, 101 (1904).

(6) For **2a**: F. D. Chattaway and A. J. Walker, *J. Chem. Soc.*, **127**, 975 (1925); R. Huisgen, E. Aufderhaar and G. Wallbillich, *Chem. Ber.*, **98**, 1476 (1965). For **2b**: Prepared according to **2a** and **2c**, m.p. 117-119°. For **2c**: N. Dieckmann and G. Platz, *Chem. Ber.*, **38**, 2989 (1905).

(7) H. Meyzr, W. Bellmann, *J. Prakt. Chem.*, [2], **33**, 21 (1886); C. König, J. Reissert, *Chem. Ber.*, **32**, 786 (1899); A. W. Murray and K. Vaughan, *J. Chem. Soc.*, 2072 (1970).